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## INVITED COMMENTARY

**Complete Ulcer Healing as a Primary Endpoint in Studies on Critical Limb Ischemia (Hoffman et al)****L. Norgren\****Department of Surgery, University Hospital Örebro, S 70185 Örebro, Sweden*

The systematic review presented in this article was prompted by the fact that the European Guidelines for drug trials in critical limb ischemia (CLI) only accept complete ulcer healing as the primary endpoint.<sup>1</sup> The use of this endpoint after revascularization was questioned. The authors concluded, after thorough review of the literature, that complete ulcer healing was reported infrequently and studies reporting this outcome had a low level of evidence; no randomized controlled trials were found.

Therefore the question is raised as to whether complete ulcer healing is the most relevant single primary endpoint for drug trials in CLI.

Patients with the most advanced stages of peripheral arterial occlusive disease (PAOD), commonly classified as Fontaine stage III and Fontaine stage IV including those with rest pain and ulcers/gangrene respectively, have a poor prognosis, with an annual mortality rate of about 20% and limited treatment options. First choice treatment is endovascular or open surgical repair, should technical prerequisites be met. The main pathophysiological findings are multi-level blocked large arteries combined with severe microcirculatory malfunction and therefore dramatic response to medical or other treatments can not be expected.

The Trans-Atlantic conference on clinical trial guidelines in PAOD<sup>2</sup> recommended the following primary endpoints for the treatment of CLI: complete relief of pain without analgesia for Fontaine stage III and complete ulcer healing of both legs for Fontaine

stage IV. In addition, amputation rate should be a primary endpoint. Partial healing of ulcers is of limited clinical significance and therefore not an acceptable endpoint. The most important primary endpoint is composite, including all-cause mortality, cardiovascular morbidity and amputation, and this was recommended to be superior to single endpoints.

Response-based endpoints were also discussed, the optimal response would be a living patient, with two legs, having no ulcers and free from pain without analgesia. With improved and refined quality of life instruments, QoL assessment also might be a relevant endpoint.

**Regulatory Authorities' Aspects**

Interestingly, the FDA does not provide published guidelines on endpoints, but usually approves amputation-free survival as the primary endpoint. Normally ulcer healing and pain relief are not approved primary endpoints.

On the other hand there is always a negotiation between the study sponsor and the FDA to decide the most valid endpoint(s) for a specific trial.

The European Guidelines<sup>1</sup> accept for Fontaine stage III trials, the concept of "complete relief of pain while off analgesics" and connects this with absence of development of ischaemic lesions.

For Fontaine stage IV trials, the European Guidelines state that "generally, patients eligible for surgical/interventional reconstruction should not be included", a fact that reduces the chance of treatment effect, due to advanced disease. As primary endpoint in stage IV, only "complete healing of all necroses and ulcerations" is accepted, while pain, consumption of

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analgesics, hemodynamics, interventions and QoL are all secondary endpoints.

The response based endpoint, patient being alive, having both legs, no wound or pain and off analgesics also is listed.

The European Guidelines also present recommendations for prevention (of ischaemic events) trials, claiming a composite endpoint to be most relevant.

### Revascularization Endpoints

As clearly shown by the authors, complete ulcer healing is rarely used as an endpoint after revascularization. It also is evident that studies to evaluate the role of a revascularization procedure are usually not designed as randomized trials with a comparator "standard" procedure. Observational studies are more common and although not providing level 1 evidence may be relevant for practical consideration of the role of the revascularization procedure under study, particularly if standard reporting criteria are used for inclusion and for outcome evaluation. An example endpoint is "limb salvage" or better a composite endpoint of event-free survival. Events should include major amputation, non-healing of ulcers, residual ischaemic pain, myocardial infarction and ischemic stroke.<sup>3</sup>

### Can Drug Trials and Revascularization Studies be Compared?

First, trials comparing drugs with revascularizations have not been performed so far! The second question is whether drug trials can be compared to revascularization trials. This is obviously difficult for several reasons, one being that included patients differ considerably: those selected for drug trials should normally be non-reconstructable (for technical reasons or due to contraindications). The multilevel vascular lesions in the leg of these patients are usually part of a generalized disease with poor prognosis. Those with reconstructable vascular lesions may have a slightly better outcome and revascularization always should be considered the first option.<sup>4</sup> Another difference is that revascularization only affects leg symptoms, while drug treatment has systemic effects. For these reasons no single endpoint is relevant for all types of treatment trials in CLI. On the other hand, composite endpoints, describing the outcome of the

patient and the leg may be reasonable to use for any treatment option used in well conducted trials.

To summarize, the authors suggest that complete ulcer healing should not be used as the single primary endpoint in drug trials for CLI and claim that having a different primary endpoint from those recommended for revascularization studies is unjustified. They propose endpoints that are "both clinically relevant and realistic and should apply to pharmacotherapy and revascularization procedures" equally, indicating that amputation-free survival, the functional status of the patient and quality of life are more appropriate alternatives. To use a composite endpoint also seems to be a good alternative, but as discussed above, this has to include complete ulcer healing. I fully agree that response-based endpoints are valuable as they will consider time to response, provided "response" is uniformly defined.

Quality of life assessment must be considered. Such parameters are very important to the patient, but require good working instruments for the symptoms and disease in question.

If, in the future, medical treatment could be directly compared with revascularization, including patients with more uniform entry criteria, the role of composite endpoints might become even more important. Requirements for such trials have to be potentially more effective medical therapies and an acceptance of delayed revascularization, where this is a potential treatment option.

### References

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